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Original Article

Elevated neurotensin levels among obese adolescents may be related to emotion dysregulation and impulsivity: a cross-sectional, case-control study

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ABSTRACT

Background. In this study, we aimed to evaluate the serum neurotensin (NT) levels and their relationships with self-reported anxiety, emotion regulation skills and impulsivity in healthy and obese adolescents.

Methods. Adolescents who gained weight between 12- 17 years of age and who were above the 95th percentile (p) for body mass index (BMI)>95p were compared with age- and gender-matched healthy adolescents with a BMI of 3-85 p. Anthropometric measurements were performed, and serum NT levels were analyzed with ELISA method in all participants. Barrat Impulsivity Scale-11 (BIS-11), Screen for Child Anxiety Related Disorders (SCARED) and Difficulties in Emotion Regulation Scale (DERS) were used for evaluating self-reported impulsivity, anxiety and emotion regulation. MANOVA with follow-up univariate ANOVAs (Bonferroni corrected) were used for group comparisons. P was set at 0.05 (two-tailed).

Results. Sixty-five obese and 65 healthy adolescents were included in the study. In the obese group, NT levels were significantly elevated compared to the control group. Self-reported emotion-regulation difficulties, anxiety and impulsivity were significantly elevated among obese adolescents. Serum NT levels among the obese group were positively correlated with emotion dysregulation and impulsivity scores.

Conclusions. In this study, we found emotional dysregulation, anxiety, impulsivity, and serum NT levels were significantly elevated among obese adolescents compared to controls. NT levels in the obese group correlated with impulsivity and emotion dysregulation. Further studies should evaluate the potential role of NT in the etiology of psychopathology among adolescents who are obese.

Key words: adolescent, anxiety, emotion regulation, neurotensin, obesity.

Obesity can affect 5.0 % of children worldwide, especially among the economically disadvantaged.[1] It may affect children across all age groups and there seems to be a temporal trend of increase within the last 40 years.[1,2] The current consensus is that pediatric obesity may arise due to interactions between biological, developmental, behavioral, genetic and environmental factors.[3] The ongoing COVID-19 pandemic may also contribute to the emergence and persistence of pediatric obesity.[4]

Neurotensin (NT) is a 13 amino acid peptide secreted from the enteroendocrine cells in the small intestine and the central nervous system.[5] It may modulate the dopaminergic, serotonergic and glutamatergic function in the nigro-striatal and meso-cortical limbic systems and may have an anorexigenic effect via the lateral hypothalamic region.[6,7] Various

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pre-clinical studies suggest that it may have a role in anorexia as a response to stress, emergence of anxiety- like behavior, hedonic eating, reward/ reinforcement and memory.[8-11] A recent review suggested that NT may have therapeutic potential[12] and another study suggested that elevated levels of its precursor may predict weight gain and associated metabolic abnormalities among children.[13] Butler et al. (2015) found that plasma NT levels were elevated among children with Prader-Willi syndrome characterized by hyperphagia via decreasing gastric motility.[14] Available studies suggest that pediatric obesity at least in a subgroup of patients may be associated with elevated levels of anxiety, impulsivity and emotional eating.[15-17]

Despite the importance of NT functioning in those constructs, no study up to now has evaluated the relationships between NT levels and anxiety, impulsivity and emotion regulation among obese children.

Therefore; in this study, we aimed

a) to compare serum NT levels among obese and healthy adolescents
b) to compare self-reported emotion regulation, anxiety and impulsivity scores among obese and healthy adolescents, and
c) to investigate the relation of NT with emotional regulation, anxiety and impulsivity among obese adolescents.

Material and Methods

Study design, center and time frame

The study was designed as a uni-center, cross-sectional, case-control study and obese and healthy adolescents aged between 12-17 years were enrolled between April 2017 and April 2018.

Inclusion Criteria and Exclusion Criteria

Patients with a body mass index (BMI) percentile of > 95 according to the WHO criteria[18] formed the obese group. Obese adolescents with a body mass index (BMI) >95 percentile and healthy adolescents with a BMI between 3 and 85 percentiles, according to the data of Turkish National Growth Charts [A], who had similar age and gender distribution and admitted for routine control were enrolled in the study.[19] Patients with underlying endocrine (hypothyroidism, Cushing syndrome, etc.) or non-endocrine (hypothalamic dysfunction, drug use, syndromic diseases) pathologies were excluded from the study. Psychiatric disorders including neurodevelopmental disorders were excluded with semi structered clinical interview via Schedule for Affective Disorders and Schizophrenia for School Age Children Present and Life-time Version (KIDDIE-SADS-PL)[20] and Diagnostic and Statistical Manual of Mental Disorders (DSM–5). Both life-time and acute psychopathology (within two months) were excluded. Ninety eight obese adolescents were evaluated with K-SADS-PL and DSM-5 criteria. 33 adolescents were excluded, 21 of the adolescents had attention deficit and hyperactivity disorder; 8 of them had anxiety disorder; 2 of the adolescents had major depressive disorder and 2 of them had obsessive compulsive disorder. The same child and adolescent psychiatrist evaluated all the adolescents in one year. She gave new appointments to adolescents for psychiatric evaluation after pediatric endocrinologic and pediatric examination. Patients with a history of intracranial operation, syndromic obesity findings (Prader Willi, Alström, Laurence–Moon-Biedle syndrome, etc.) or a genetic cause for monogenic obesity (leptin gene defect, leptin receptor defect, etc.), an active infection, evidence of hypothalamic dysfunction, a history of pregnancy or lactation that can affect OXT release, and who were not willing to participate in the study were also excluded.

Adolescents who applied to the general pediatrics outpatient clinic for any complaints, who were similar to the obese group in terms of age and gender, without chronic diseases, and whose BMI percentile were between 3-85 were included in the healthy control group.

Anthropometric Evaluation

Height (cm), body weight (kg) and waist circumference (cm) of all cases included in the study were measured after an overnight fast in the morning. The height was measured with the Harpenden stadiometer (Holtain Ltd., Crosswell, Wales, UK) with a measurement accuracy of 0.1 cm, and the body weight was measured with a SECA scale (SECA Medizinische Messsysteme und Waagen, Hamburg, Deutschland) with a measurement sensitivity of 0.1 kg after all clothes were removed except underwear.

The BMI is calculated by dividing body weight in kilograms (kg) by height in meters squared (m2) and it is expressed as kg/ m2. The website www.ceddcozum.com, developed by the Turkish Pediatric Endocrinology and Diabetes Association, was used to calculate percentile and standard deviation scores for weight, height, head circumference, and BMI according to Olcay Neyzi[19], CDC and WHO references. BMI SDS was calculated for all children aged 12-17 years included in the study.

Blood Samples

Blood samples were taken after a minimum of 12 hours of fasting. Serum NT levels were studied using the firm's original reactives with standardized methods on Architect AU5800 (Beckman Coulter, Brea, CA, USA) analyzer on serum samples kept at -80°C. Serum was analyzed with NT (Neurotensin (Human, Rat, Mouse)- EIA Kit, 96 wells, CAT No:EK-048-03, Phoenix Pharmaceuticals) using enzyme-linked immunosorbent assay (ELISA) method.

Psychiatric Evaluation

Sociodemographic Data Form: This form was prepared to collect information about sociodemographic characteristics of children and parents and completed by the clinicians.

Schedule for Affective Disorders and Schizophrenia for School Age Children Present and Life-time Version (KIDDIE-SADS-PL): It is a semi-structured interview form which was developed by Kauffman et al. in order to examine present and life-time psychopathology in children and adolescents aged between 6-18 years.[20] Turkish translation and reliability and validity study of KIDDIE-SADS-PL were carried out by Gökler et al., in 2004.[21]

Difficulties in Emotion Regulation Scale (DERS): Gratz and Roemer developed DERS in order to measure difficulties in emotion regulation.[22] The scale has six subscales including awareness, clarity, non-acceptance, strategies, impulse, and goals. Higher scores indicate the existence of difficulty in the regulation of stronger emotions. Turkish adaptation, reliability and validity study of the scale was conducted by Ruganсı et al., in 2010.[23] Adolescents completed the DERS forms in this study. Confirmatory Factor Analyses of the DERS was evaluated in Turkish adolescents.[24] This scale has been used in various studies in Turkish adolescents.[25,26]

The Screen for Anxiety-Related Emotional Disorders (SCARED): This instrument consists of 41 Likert-type items evaluating symptoms of anxiety over the previous three months and has parent/ caregiver and child versions.[27] The Turkish reliability and validity study was conducted by Çakmakçı, in 2004.[28] Both child and parent's report were used in this study.

Barratt Impulsiveness Scale-11 (BIS-11): BIS-11 was developed by Barratt to evaluate motor, attentional and cognitive facets of impulsivity. Elevated scores denote greater impulsivity.[29] Turkish validity and reliability study of BIS-11 was conducted by Güleç et al., in 2008.[30] Adolescents completed BIS-11 in this study. It has been used in various studies on adolescents in Turkey.[31,32]

Ethics Approval

IRB approval was granted by the İzmir Katip Çelebi University Faculty of Medicine Clinical Research local Ethics Board (Date:13.09.2017 Approval Number:193). Written informed consent of adolescents and their parents were procured prior to study participation and all study procedures were in accordance with the Declaration of Helsinki and local laws and regulations.

Sampling size (Power analysis)

G*Power Version 3.0.10 was used for statistical power analysis.[33] Since there were no similar studies in literature, regarding the difference between two mean values at a moderate level and taking effect size as 0.5 (using cohen criteria), alpha as 0.05 and power as 0.80, the total sample size was determined as 128 adolescents with equal number of obese youth and controls.

Statistical analysis

Statistical analyses were conducted with SPPS 24.0 (IBM Inc., ChicaArmonk, NY, USA) program. Assumptions of normality were evaluated with Kolmogorov-Smirnov test. Quantitative variables were summarized as means and standard deviations. Comparison of multiple dependent variables across groups was conducted with MANOVA (via Pillai's trace) followed with univariate ANOVAs (Bonferroni corrected). DERS, BIS-11 and SCARED domains of adolescents with obesity and control adolescents along with NT levels were compared with MANOVA. Due to non-normal distribution, lack of equality of error variances for several subscales (Levene's test, DERS-nonacceptance p=0.001, DERS-impulsivity p=0.004, DERS-strategy p=0.03, DERS-clarity p<0.001, all BIS-11 subscales, SCARED-child form and neurotensin p<0.001), Pillai's trace was used to evaluate results. Chi-square test was used for the comparison of nominal variables across groups. Spearman's rank order correlation analyses were conducted to evaluate relationships between quantitative variables. Partial correlations were used to control for effects of age, gender and BMI. P was set at 0.05 (two-tailed).

Result

A total of 65 obese (mean age 14.6 ± 1.4 years, 32 female) and 65 healthy adolescents (control group) (mean age 14.6 ± 1.5 years, 32 females) were included in the study. The groups did not differ significantly in terms of gender and mean age. BMI, BMI- SDS and NT levels of obese youth and the controls are shown in Table I (for each, p<0.001).

DERS, BIS-11 and SCARED scores according to groups is illustrated in Table II. In MANOVA, the effect of diagnosis (F = 52.179, p= 0.000, partial $\eta 2$= 0.84] was significant while results for univariate ANOVAs are presented in Table III.

For pair-wise comparisons, adolescents with obesity had significantly elevated scores in DERS-clarity (p= 0.000, 95% CI= 1.6-3.5), DERS-goal (p=0.000, 95% CI= 3.5-6.0), DERS-strategy (p=0.000, 95% CI= 6.7-10.7), DERS-impulsivity (p=0.000, 95% CI= 5.5-8.7), DERS-nonacceptance (p=0.000, 95% CI= 2.9-6.2), DERS-awareness (p=0.000, 95% CI= 2.5-4.6), DERS-total score

Table I. Demographic characteristics, BMI and neurotensin levels between obese and healthy adolescents.

	Obese Group (*n=65*) mean± SD	Control Group (*n=65*) mean± SD	Statistics (p value)
Age (years)	14.6±1.4	14.6±1.5	0.976
Sex (male/ female)	32/33	32/33	1.000
BMI (kg/m^2)	35.5±4.4	20.8±2.1	<0.001
BMI SDS	3.1±0.6	-0.02±0.7	<0.001
Neurotensin (ng/ml)	0.61±0.39	0.40±0.11	<0.001

BMI: body mass index, BMI SDS: body mass index standard deviation score

Table II. Comparisons of DERS, BIS, SCARED subscale scores of obese and healthy adolescents.

	Obese Group (*n=65*) mean± SD	Control Group (*n=65*) mean± SD
DERS subscales		
Clarity	12.36±2.69	9.72±2.67
Goal	17.24±3.45	12.50±3.48
Strategy	20.81±6.53	12.04±4.03
Impulsivity	19.29±5.18	12.23±3.32
Non-acceptance	15.33±5.17	10.80±3.62
Awareness	16.07±3.51	12.40±1.59
Total score	101.14±16.52	69.70±9.27
BIS-11 subscales		
Attentional impulsivity	19.24±3.75	11.86±2.86
Motor impulsivity	24.52±2.67	17.09±5.03
Non planning	23.40±2.22	15.89±4.13
Total Impulsivity	67.16±5.30	44.84±10.30
SCARED scores		
SCARED child	26.90±10.07	6.66±4.53
SCARED parent	26.37±10.70	6.38±5.14

DERS: difficulties in emotion regulation scale, SCARED: the screen for anxiety-related emotional disorders, BIS-11: barratt impulsiveness scale-11

Table III. Effect of obesity diagnosis on domains of emotion regulation difficulties, impulsivity, neurotensin levels and severity of anxiety symptoms.

Independent variables	Dependent Variables	Univariate F	dF	P*	Partial η2
Obese vs. Control	DERS Clarity	27.8	(1,119)	0.000	0.190
	DERS Goal	54.8	(1,119)	0.000	0.315
	DERS Strategy	74.3	(1,119)	0.000	0.384
	DERS Impulsivity	76.3	(1,119)	0.000	0.391
	DERS Nonacceptance	30.2	(1,119)	0.000	0.203
	DERS Awareness	48.8	(1,119)	0.000	0.291
	DERS Total score	157.4	(1,119)	0.000	0.569
	BIS Attentional impulsivity	143.0	(1,119)	0.000	0.546
	BIS Motor impulsivitiy	94.1	(1,119)	0.000	0.442
	BIS Non planning	151.6	(1,119)	0.000	0.560
	BIS Total Impulsivity	214.2	(1,119)	0.000	0.643
	Neurotensin	17.1	(1,119)	0.000	0.126
	SCARED-Child form	199.7	(1,119)	0.000	0.627

DERS: difficulties in emotion regulation scale, SCARED: the screen for anxiety-related emotional disorders, BIS-11: barratt impulsiveness scale-11.
*Bonferroni corrected.

(p=0.000, 95% CI= 26.3-36.2), BIS-11-attentional impulsivity (p=0.000, 95% CI= 6.2-8.6), BIS-11-motor impulsivity (p=0.000, 95% CI= 5.7-8.6), BIS-11-non planning (p=0.000, 95% CI= 6.3-8.7), BIS-11-total impulsivity (p=0.000, 95% CI= 19.0-25.0), neurotensin (p=0.000, 95% CI= 0.1-0.3) and SCARED-child form (p=0.000, 95% CI= 17.4,23.0; all Bonferroni corrected).

In obese and control groups, serum NT level was found to be positively correlated with all BIS and DERS subscales and total scores (p <0.05). After adjustment for age, gender, and BMI, the positive correlation among NT and BIS attentional, non-planning and total impulsivity scores, DERS strategy, impulsivity and total scores persisted; however, the relationship between serum NT level and BIS motor impulsivity, DERS goal, clarity, non-acceptance, awareness disappeared (Table IV).

Discussion

This uni-center, cross-sectional, case-control study evaluated NT levels along with self and parent–reported anxiety, self-reported impulsivity and emotion regulation problems and the relationships among those constructs in adolescents with obesity and age and gender-matched controls. As a result, NT levels were found to be significantly elevated along with impulsivity, anxiety and emotion regulation problems among adolescents with obesity. NT levels correlated significantly with cognitive and attentional impulsivity and impulsivity while trying to regulate emotions after adjusting for BMI, age and gender.

Various pre-clinical and clinical studies suggest an important role for NT in emergence of obesity.[10,12,34] Butler and colleagues reported that plasma NT levels were elevated among children with Prader-Willi syndrome characterized by hyperphagia[14] and obesity while Barchetta and colleagues (2020) reported that plasma pro-NT levels may predict weight gain and associated metabolic abnormalities among children.[13] A previous study by the same group suggested that NT may also be a biomarker of insülin-resistance and problems in metabolism.[35] Our results support those reported previously and suggest that elevations in NT levels may be associated with adolescent obesity. However, as NT levels were also elevated among children

Table IV. Correlations of serum NT levels (ng/mL) with self-reported impulsivity, self- and parent- reported anxiety, self-reported emotion regulation and anthropometric parameters.

	All subjects *(n=130)*		All subjects *(n=130)*	
	Spearman's Rho	**p*	*Partial Correlation*	***p*
Age (years)	-0.088	0.322		
Gender	0.041	0.643		
BMI (kg/m^2)	0.293	*0.001*		
BIS Attentional impulsivity	0.523	*<0.001*	0.472	*<0.001*
BIS Motor impulsivity	0.303	*<0.001*	0.142	0.128
BIS Non planning	0.387	*<0.001*	0.262	0.004
BIS Total Impulsivity	0.447	*<0.001*	0.346	*<0.001*
DERS Clarity	0.178	*0.043*	0.050	0.590
DERS Goal	0.308	*<0.001*	0.172	0.064
DERS Strategy	0.344	*<0.001*	0.202	*0.029*
DERS Impulsivity	0.375	*<0.001*	0.249	*0.007*
DERS Non-acceptance	0.286	*0.001*	0.163	0.079
DERS Awareness	0.241	*0.006*	0.097	0.300
DERS Total score	0.413	*<0.001*	0.286	*0.002*
SCARED Child score	0.171	0.061	-0.080	0.390
SCARED Parent score	0.105	0.074	-0.163	0.078

DERS: difficulties in emotion regulation scale, SCARED: the screen for anxiety-related emotional disorders, BIS-11: barratt impulsiveness scale-11

*Spearman's correlation analysis; Serum NT level as dependent variable

** Partial correlation coefficient; controlling for age, gender and BMI.

with coeliac disease and among patients with disrupted renal functioning[36,37], elevations in NT may be due to increased gastro-intestinal permeability, low grade inflammation or changes in renal function, rather than obesity *per se*. Further studies on obese adolescents may also evaluate renal functioning and inflammatory markers or use gastro-intestinal endoscopy along with NT levels to elucidate the contribution of those factors.

Previous studies suggest that pediatric obesity at least in a subgroup of patients may be associated with elevated levels of anxiety, impulsivity, emotion regulation problems and emotional eating.[15-17] Supporting those views, Sezer Efe and colleagues found that social anxiety and emotional eating were elevated and displayed positive correlations among obese adolescents.[38] Yilmaz Kafali and colleagues found that although emotion regulation problems were elevated among obese adolescents, unhealthy life-style practices such as internet addiction and emotional eating mediated the effects of those problems on obesity.[39] Sönmez and colleagues found that inattention, hyperactivity and impulsivity symptoms were elevated among obese children and adolescents.[40] A study employing ecological momentary assessment suggested that impulsivity may contribute to dysregulated eating among over-weight and obese youth.[41] The results of our study also support those reported previously and suggest that emotion regulation problems, impulsivity and self- and parent-reported anxiety were significantly elevated among obese adolescents. Due to a lack of evaluating life-style practices and emotional eating patterns among our sample and due to the cross-sectional design of our study we could not offer hypotheses on causality and mediation. Further studies may employ larger samples and prospective designs to evaluate the differential contributions of those constructs to the emergence and persistence of pediatric obesity.

Pre-clinical studies suggest that NT may have a role in regulation of stress and anxiety, hedonic eating, reward/ reinforcement and memory.[8-11] Furthermore, recent studies suggest that NT may be involved in cognitive changes associated with obesity.[42,43] Despite those promising studies, no study up to now evaluated the relationships between NT levels and anxiety, impulsivity and emotional dysregulation among obese adolescents. We found that NT levels correlated significantly with emotion dysregulation and all facets of impulsivity. NT levels correlated significantly with cognitive and attentional impulsivity and impulsivity while trying to regulate emotions after adjusting for BMI, age and gender. The correlations between serum NT level and BIS motor impulsivity, DERS goal, clarity, non-acceptance, awareness disappeared after adjusting for age, gender and BMI, while others remained unchanged. Although the cross-sectional nature of our study precludes hypotheses about causality, those findings may suggest a role of BMI, age and gender in NT levels. Also, effects of NT on motor impulsivity, DERS-goal, clarity, non-acceptance and awareness may partially overlap with emotional eating and binging. Our results may support a role of NT in emotional and cognitive symptoms associated with obesity which may be primarily due to impulsivity. Previous reports on association of impulsivity with changes in dopaminergic functioning and inhibition of D2R signaling by neurotensin may also support this hypothesis.[44,45] However, this hypothesis should be evaluated with further pre-clinical and clinical studies evaluating the role of NT and its precursors in impulsivity and obesity.

Our results should be evaluated within their limitations. Firstly, the precursor of NT, pro-NT is more stable and has a longer half-life than NT and our results may be further enriched had we measured this precursor along with NT. Secondly; our results are valid only for adolescents evaluated within the specified time-frame at the study centers who were free of endocrine and genetic etiologies and they may not be generalized to other patients or obese adolescents in the community. Thirdly, NT levels may interact with growth hormone levels and may change during puberty and our results sohuld be replicated with obese children and adults.[46] Fourth, we did not evaluate the role of NT in emotional eating and further studies on the role of NT in pediatric obesity may use age-appropriate questionnaires (e.g. Child-Three Factor Eating Questionnaire) to evaluate it.[47] Fifth, NT levels may also depend on renal function, integrity of the gastro-intestinal mucosa and low grade inflammation[36,37] and further studies are needed to evaluate the contributions of those factors to elevations of NT in pediatric obesity. Sixth, we did not evaluate for the effects of exercise, diet and binge eating.[48,49] Seventh; there may be distinct patterns of pediatric obesity according to change in BMI through development and the relative contribution of NT may differ across those groups.[50] Eighth, while determining the exclusion criteria, some psychiatric disorders were diagnosed according to DSM-IV (with help of K-DSADS-PL) and some disorders (e.g., neurodevelopmental disorders) according to DSM-5 criteria. Lastly, although the DERS and BIS-11 scales are used in many studies in adolescents, there is no validity and reliability study in the adolescent age group. Longitudinal studies may illustrate the role of NT in developmental subgroups of pediatric obesity.

Regardless of its limitations, our results suggest that circulating NT levels may be elevated among obese adolescents along with anxiety, impulsivity and emotion dysregulation. Also, NT levels may correlate significantly with various facets of impulsivity.

Overall, NT signaling could be an important target for pharmacotherapeutic interventions for psychiatric problems in obesity.

Ethical approval

IRB approval was granted by the İzmir Katip Çelebi University Faculty of Medicine Clinical Research Local Ethics Board (Date:13.09.2017 Approval Number:193).

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: GÖ, GC, YÖ, TK, BND; data collection: GÖ,YÖ,GÇ; analysis and interpretation of results: GÖ, BND, AET, GÇ; draft manuscript preparation: GC,TK, AET. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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